

Oligometastatic non-small cell lung cancer (NSCLC)

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Editorial

Oligometastatic non-small cell lung cancer (NSCLC): Does number of metastasis matter?



Synchronous oligometastatic (sOM) status is perceived as a distinct disease from polymetastatic presentation, with a potential higher overall survival (OS) probability when treated with local radical treatment (LRT).

Recently, the long-term outcomes of the practice changing phase II randomized trial on sOM non-small cell lung cancer (NSCLC) were published [1]. Forty-nine patients with up to 3 metastases (primary tumor excluded) after first line systemic therapy were randomized to either LRT (i.e. radiotherapy or surgery) to all disease sites or

maintenance systemic therapy (MT)/observation (O). This trial demonstrated that LRT improved OS, median 41.2 months (95 % CI, 18.9 months to not reached) in LRT and 17.0 months (95 % CI, 10.1–39.8 months) in MT/O ($p = 0.017$). These results supported the integration of LRT in sOM-NSCLC and its implementation in daily clinical practice.

However, despite some consensus about sOM status, a uniform definition does not exist as reported in a systematic review performed by the European Organization for the Research and Treatment of Cancer (EORTC)

Table 1

Article included in the systematic review [2] and current literature [3,4].

Articles	Number of patients	Maximal number of metastases defined	Maximal number of metastases treated	Patients with ≤ 2 metastases treated (%)	Patients with ≥ 3 metastases included (%)
Downey R. 2002	23	1	1	100%	0%
Khan A. 2006	23	2	2	100%	0%
Inoue St et al. 2010	25	5	5	N.A.	N.A.
Cheruvu P. 2011	38	8	8	N.A.	N.A.
Collaud S. 2012	29	1	1	100%	0%
Congedo M. 2012	53	2	2	100%	0%
De Ruysscher D. 2012	40	5	3	97.4%	2.6%
Lopez Guerra J. 2012	78	4	4	91%	9%
Griffioen G. 2013	61	3	3	96.7%	3.3%
Nieder C.S. 2014	23	3	2	100%	0%
Parikh R. 2014	186	5	5	74%	26%
Sheu T. 2014	90	3	3	88%	12%
Plones T. 2015	56	5	4	99%	1%
Su Ss. 2015	198	3	3	56%*	44%*
Xanthopoulos E. et al. 2015	25	4	4	84%	16%
Fleckenstein J. 2016	39	5	5	90%	10%
Johnson K. 2016	37	5	N.A.	N.A.	N.A.
Sakai Ks. 2016	18	5	N.A.	N.A.	N.A.
Su Ss. 2016	91	4	N.A.	N.A.	N.A.
Iyengar P. 2017	29	5	3	93%**	7%
Gomez D. 2019	49	3	3	98%	2%
Bauml JM. 2019 [3]	51	4	4	94%	6%
Arrieta O. 2019 [4]	37	5	N.A.	65%	35%

*56 % with single metastasis, 44 % ≥ 2 metastases; ** 14 patients received a LCT (randomized trial); N.A.: not available.

lung cancer group (LCG) [2]. Specifically, EORTC (in collaboration with European Society for radiotherapy and oncology – ESTRO) is promoting an ongoing trial (E²-RADIatE-OligoCare) including sOM and oligorecurrent patients with the primary outcome to identify patient, tumour (NSCLC, breast, prostate and colon-rectal cancers) staging and treatment characteristics impacting in OS.

About the systematic review, the aim was to provide an overview of sOM-NSCLC definition from reported series and trials [2]. The maximum number of metastases ranged from 1 to 8 in 21 selected articles [2]. Additionally, the definition of sOM-NSCLC in prospective clinical trials is also heterogeneous and vary between 1 and 6 [2–5]. Further, 74–100% of 1211 included in the systematic review patients had ≤2 metastatic sites. Furthermore, total numbers of metastases detected and treated were not described in 5 (24 %) studies, restricting clinical interpretation on the role of LRT (Table 1). In the recent randomized Gomez *et al.* trial, inclusion criteria allowed up to three metastases but the majority of patients (65 %) had only 0–1 [1].

Not surprisingly, the field is moving towards allowing higher number of metastases in clinical trials, as technically LRT is feasible for an increasing number of sites.

Recently, the EORTC-LCG published a consensus about the maximal number of metastases allowed to define sOM-NSCLC. Authors evaluated sOM-NSCLC definitions in daily clinical practice in Europe, by a survey and discussion of ten real life cases [7,8]. In the survey, the maximum number of metastases considered as sOM-NSCLC was again variable and 42 % of responders identified 3 as the correct definition [7]. Then analyzing real life cases, sOM-NSCLC was conservative and linked to radical intent of treatment. Members of the consensus meeting concluded that the maximum number of metastases is depending on the possibility to offer a LRT strategy [6].

Finally, based on the systematic review, most studies did not specify the local nodal status (N-status), although it is known that advanced N-status is associated with lower OS [7]. In the Gomez *et al.* trial, besides LRT, only number of metastases and presence of a driver alteration were associated with improved OS [1]. N2/N3 disease was non-significant in OS, probably due to the limited number of enrolled patients. As even, in Gomez *et al.* not all patients benefited from LRT and a correct selection is advocated. The ongoing SARON trial (NCT02417662) could provide answers, as patients will be stratified according to mediastinal N-status (N 0-1 vs N2-3), histology (adeno- vs non-adenocarcinoma), brain metastases (present vs absent) and number of oligometastatic sites (1 vs 2 vs 3). Other factors such as circulating tumour DNA and molecular signatures should be evaluated in future trials [10,11].

In order to select sOM-NSCLC patients, accurate radiological and pathological staging (preferably including molecular characterization) is needed [9]. Therefore, as described in EORTC articles [2,5], ¹⁸F-DG-PET-CT, brain MRI-scan and a possible pathological proof of a

metastasis are necessary. The promising data about immunotherapy and radiation combination are inspiring new sOM-NSCLC trials, investigating the association of these treatments [3]. Hence, a single definition and recommended staging work-up are crucial.

The EORTC LCG approach is based on a secure methodology, because expert team carried out the systematic review, while survey and clinical cases discussion contributed on basic scenario about sOM-NSCLC treatment in Europe. Finally, a consensus meeting was held. Based on findings coming from the previous 3 steps, proposals were discussed and definitions were consensually agreed between scientific societies involved in lung cancer treatment (surgeon, pneumologist, radiation and medical oncologist) [6]. The EORTC LCG consensus definition is a good starting point for future clinical trials selecting the correct patient for the fit oncological treatment [5].

Contributors

All Authors contributed equally.

Declaration of Competing Interest

None.

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